

# Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study

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**BACKGROUND AND OBJECTIVES:** There is a high rate of consanguinity in Saudi Arabia; however, information on its relationship with genetic disorders is limited. The objective of this cross-sectional study was to explore the role of consanguinity in genetic disorders.

**SUBJECTS AND METHODS:** The study sample was determined by a multistage probability random sampling procedure. Consanguinity status was obtained during household visits. Primary care physicians performed a history and physical examination of all children and adolescents younger than 19 years, and all cases of genetic diseases were recorded. The chi-square test was used to compare proportions.

**RESULTS:** During the two-year study period (2004-2005), 11 554 of 11 874 (97%) mothers answered the question on consanguinity, and 6470 of 11 554 (56%) were consanguineous. There was no significant association between first-cousin consanguinity and Down syndrome ( $P=.55$ ). Similarly, there was no significant association with either sickle cell disease ( $P=.97$ ) or glucose-6-phosphate dehydrogenase deficiency ( $P=.67$ ) for first-cousin consanguinity. A borderline statistical significance was found for major congenital malformations ( $P=.05$ ). However, the most significant association with first-cousin consanguinity was congenital heart disease (CHD) ( $P=.01$ ). Finally, no significant association was found for type 1 diabetes mellitus ( $P=.92$ ). For all types of consanguinity, similar trends of association were found, with a definite statistically significant association only with CHD ( $P=.003$ ).

**CONCLUSION:** The data suggest a significant role of parental consanguinity in CHD. However, a relationship between consanguinity and other genetic diseases could not be established. The effect of consanguinity on genetic diseases is not uniform and this should be taken into consideration in genetic counseling.

Consanguineous marriages are common in many Middle Eastern countries, with first-cousin types being the most common. To cite only a few examples: The reported prevalence of consanguinity in Jordan was 51.3%;<sup>1</sup> in Qatar, 54.0%;<sup>2</sup> in the United Arab Emirates, 50.5%;<sup>3</sup> and in Yemen, 40%.<sup>4</sup> In Saudi Arabia, reports from Saudi cities such as Riyadh and Dammam indicated prevalence rates of 51.3% and 52.0%, respectively.<sup>5,6</sup> However, El-Hazmi et al reported the first national consanguinity prevalence of 57.7%, with first-cousin marriages being the most frequent.<sup>7</sup> In a more recent survey of a representative sample of Saudi families defined by a multistage random sampling procedure representing both urban and rural settlements,

the prevalence of consanguinity was 56%, with the first-cousin type the most common.<sup>8</sup>

Some populations, especially Arabs, have substantially higher genetic diseases than non-Arabs.<sup>9</sup> In some countries in the Middle East, Down syndrome has been reported to occur more commonly than in industrialized countries,<sup>10</sup> whereas blood diseases, including hemoglobinopathies, are more common in others.<sup>11</sup> Multifactorial conditions such as congenital malformations have also been reported to occur more commonly in the Middle East region and to be responsible for high morbidity and mortality.<sup>12-14</sup>

In Saudi Arabia, the prevalence of Down syndrome has been reported to be 1.8 per 1000 live births.<sup>15</sup> Sickle

cell disease (SCD) is endemic in certain regions of the country, with a prevalence ranging between 91 and 99 per 10 000 live births in the Eastern Province.<sup>16,17</sup> Similarly, there are areas of increased prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency where a prevalence of 20 per 1000 births has been reported.<sup>18</sup> However, apart from isolated reports, data on the prevalence of major congenital malformations are lacking. For example, although the pattern of congenital heart disease (CHD) has been reported, the prevalence remains unknown.<sup>19,20</sup> A prevalence of infantile hydrocephalus between 0.81 and 1.6 per 1000 live births has been reported,<sup>21,22</sup> which is higher than most reports from other countries.

Studies on the relationship between consanguinity and genetic disorders as a whole have been reported from many parts of the world. However, there are only a few reports from Saudi Arabia,<sup>5-7</sup> where a high prevalence of consanguinity and many genetic disorders coexist. Therefore, the objective of this study was to explore the potential effects of parental consanguinity on the occurrence of common genetic disorders in Saudi Arabia.

## SUBJECTS AND METHODS

Participants were selected by multistage random probability sampling of Saudi households from each region of the country.<sup>23</sup> This cross-sectional sample was used for the assessment of physical growth.<sup>23</sup> A questionnaire was designed for this purpose and administered to the mother, father, or both during household visits. The mother in each household was asked about the relationship to her husband, with a choice of one of three answers: first-degree cousin (including all four types), more distant relationship, or no relationship. Also, primary care physicians performed a history and physical examination of all children and adolescents younger than 19 years, and all cases of genetic diseases, including malformations, were recorded. For the purpose of this study, genetic disorders were classified into chromosomal, single-gene, and multifactorial defects. The commonest disorder in each category was used for the study of the effects of consanguinity. Accordingly, in this study, chromosomal disorders were represented by Down syndrome, single-gene defects by SCD and G6PD deficiency, whereas congenital malformations and type 1 diabetes mellitus are two examples of multifactorial disorders. The data were analyzed using the SPSS software package (SPSS, Chicago, IL, USA), and the chi-square test was used to compare proportions of cases in first-cousin consanguineous and nonconsanguineous groups. A statistically significant difference

was assumed when the *P* value was less than .05.

## RESULTS

During the 2-year study period (2004-2005), 11 554/11 874 (97%) of the mothers answered the question on consanguinity, and 6470/11 554 (56%) were consanguineous. First-degree cousins were the commonest relationship, accounting for 3882/6470 (60%). The diagnosis of genetic disorders was usually reached by specialists and was known to the families, most of whom had medical reports. In only a few cases the diagnosis was made by the field team physicians by means of history and physical examination. The pattern of genetic diseases for all consanguineous and nonconsanguineous couples in the study sample is shown in Table 1. The highest proportion is represented by congenital malformations, accounting for 119 genetic disorders (77 in consanguineous and 42 in nonconsanguineous families). SCD, an autosomal recessive condition, and G6PD deficiency, an X-linked recessive disorder, were the commonest examples of single-gene defects. Finally, the commonest chromosomal anomaly found in this survey was Down syndrome, occurring in 30 families. The pattern of congenital malformations and parental consanguinity is presented in Table 2, indicating that CHD was the commonest type, accounting for 68% of cases. Table 3 shows an estimate of the risk of genetic disorders relative to first-cousin consanguinity. The data show that there was no significant association between parental consanguinity and Down syndrome ( $P=.55$ ). Similarly, there was no statistically significant effect of parental consanguinity on either SCD or G6PD deficiency ( $P=.97$  and  $.67$ , respectively). There was a borderline significant association between first-cousin consanguinity and malformations ( $P=.05$ ). However, when families of children with congenital heart disease were analyzed separately, there was a statistically significant risk of first-cousin consanguinity and the occurrence of CHD in children ( $P=.01$ ). Finally, there was no significant association of first-cousin consanguinity with type 1 diabetes mellitus ( $P=.92$ ). Table 1 depicts the results of an analysis of consanguinity among all participants, indicating similar results to those for first-degree cousins, with a *P* value close to statistical significance for malformations ( $P=.067$ ) and a clearly significant association with CHD ( $P=.003$ ).

## DISCUSSION

Theoretically, consanguineous marriages have a relatively higher risk of producing offspring with genetic damage than that of the general population. Accordingly, the occurrence of genetic diseases should be higher in consan-

**Table 1.** Parental consanguinity and genetic diseases in children from all participants.

Variable	Consanguineous n=6470 (%)	Nonconsanguineous n=5084 (%)	Odds ratio (95% confidence interval)	P value
Down syndrome	21 (0.032)	9 (0.018)	1.83 (0.80-4.32)	.173
Sickle cell disease	33 (0.051)	24 (0.047)	1.08 (0.62-1.89)	.876
G6PD deficiency	23 (0.036)	21 (0.041)	0.86 (0.46-1.62)	.729
Congenital malformations	77 (0.119)	42 (0.083)	1.45 (0.98-2.15)	.067
Congenital heart disease	59 (0.091)	22 (0.043)	2.12 (1.27-3.57)	.003
Type 1 diabetes mellitus	28 (0.043)	15 (0.029)	1.47 (0.76-2.89)	.292

**Table 2.** Pattern of major congenital malformations and parental consanguinity.

Type of malformation	Consanguineous	Nonconsanguineous	Number (%)
Congenital heart disease	59	22	81 (68.1)
Congenital hip dysplasia	5	7	12 (10.1)
Hydrocephalus	5	5	10 (8.4)
Neural tube defects	2	2	4 (3.3)
Others <sup>a</sup>	6	6	12 (10.1)
<b>Total (%)</b>	<b>77 (64.7)</b>	<b>42 (35.3)</b>	<b>119 (100)</b>

<sup>a</sup>Includes scolioses, 2; talipes equinovarus, 1; cleft lip and palates, 3; esophageal atresias, 3; congenital diaphragmatic hernias, 2; and imperforate anus, 1.

**Table 3.** First-cousin consanguinity and genetic diseases in children.

Condition	First cousins n=3882 (%)	Nonconsanguineous n=5084 (%)	Odds ratio (95% confidence interval)	P value
Down syndrome	10 (0.026)	9 (0.018)	1.46 (0.55-3.89)	.55
Sickle cell disease	19 (0.049)	24 (0.047)	1.04 (0.54-1.97)	.97
G6PD deficiency	13 (0.033)	21 (0.041)	0.81 (0.38-1.69)	.67
Congenital malformations	49 (1.26)	42 (0.083)	1.53 (0.99-2.37)	.05
Congenital heart disease	34 (0.088)	22 (0.043)	2.03 (1.15-3.60)	.01
Type 1 diabetes mellitus	11 (0.028)	15 (0.029)	0.96 (0.41-2.21)	.92

guineous marriages. In countries such as Saudi Arabia, with a high consanguinity rate, it is tempting to blame consanguinity as one of the causes of conditions with a genetic basis without proof of causation. This study is an attempt to clarify the role of consanguinity as a risk factor in the occurrence of genetic diseases. In view of the fact that the first-cousin type is the closest form of consanguinity, the likelihood of detecting an effect will be greater when considering the effects of first-cousin

rather than all types of consanguinity. Nevertheless, the effect of consanguinity, in all participants, first-cousin and otherwise, was also determined and showed a trend in the level of significance of association similar to that of the first-cousin relationships.

It is common to classify genetic diseases as chromosomal, single-gene, or multifactorial defects. In this report, the commonest example of each category was used. Down syndrome was the commonest chromosomal dis-

ease found in our study; therefore, it was selected to examine the effect of consanguinity. Although the rate of consanguinity is high in parents of children with Down syndrome, it was also high in controls, resulting in the absence of a statistically significant association of parental consanguinity on the occurrence of Down syndrome in children. It can be argued that our sample size was too small to detect any significant difference. Although this may be true, our findings are similar to those of most others who reported on more patients. In a study from India on the effects of consanguinity on 417 cytogenetically confirmed Down syndrome patients, the authors concluded that consanguinity does not predispose to Down syndrome.<sup>24</sup> Another study conducted in Palestinian Arabs found that parental consanguinity was present in only 53/118 (45%) of the children with nondisjunction Down syndrome, and a similar proportion of parental consanguinity, 18/37 (48.6%), was found in other chromosomal aberrations, giving a rate of consanguinity of 45.8% (71/155) for both groups.<sup>25</sup> It appears, therefore, that parental consanguinity is not a risk factor for the occurrence of Down syndrome, a finding that is expected in view of the genetics of this syndrome.

Regarding genetic diseases caused by single-gene defects: SCD and G6PD deficiency were the commonest disorders identified in this study. SCD is found mainly in two regions of Saudi Arabia, the Eastern Province and the southwestern regions. However, because of population mobility, SCD patients and carriers of the gene are found in all regions of the country. Theoretically, the offspring of consanguineous marriages should be at higher risk of having SCD because of the autosomal recessive nature of inheritance of a common trait. However, our data showed no significant difference between the prevalence of parental consanguinity in families of children affected with SCD and that in controls. Although we could not find reports on the effects of consanguinity on SCD, this finding contrasts with those of others reporting a significantly higher effect of consanguinity on other autosomal recessive disorders. In the study on Palestinians cited above,<sup>25</sup> the prevalence of consanguinity was high in families with beta-thalassemia (84% [64/76]), cystic fibrosis (89% [24/27]), and familial recessive deafness (85% [23/27]). One possible explanation of the lack of effect of parental consanguinity in our study is the fact that in areas of increased prevalence of SCD, and an even higher prevalence of the sickle cell trait, marriages are as likely to occur between relatives and nonrelatives who might be carriers of the sickle cell trait. Such marriages are often restricted for ethnic or tribal considerations. Furthermore, this find-

ing is consistent with the notion that the risk of expression of an autosomal recessive disorder in the progeny of consanguineous unions is inversely proportional to the prevalence of carriers in the general population.<sup>26</sup> For G6PD deficiency, which is very common in almost the same areas as SCD, our findings are similar to those of others, suggesting no difference in the frequency of consanguineous marriages among the parents of individuals affected with dominant and X-linked recessive disorders and the general population.<sup>25</sup> Accordingly, because the disease is restricted to certain ethnic groups in defined areas of the countries, the same explanation of our finding of no increased prevalence of consanguinity in parents of children with this disease may also apply to cases of G6PD deficiency.

The role of consanguinity in congenital malformations has been studied by several authors from countries where the consanguinity rate is high.<sup>12,14,27-29</sup> In our study, there was a higher proportion of consanguinity in the parents of children affected with these defects, reaching what might be considered a borderline statistical significance ( $P=.05$ ). Despite clear differences in the pattern and proportions of malformations in this study, such a finding is similar to those of most reports on the subject. In two reports from the United Arab Emirates, one found that congenital anomalies were significantly higher in the offspring of consanguineous couples ( $P<.001$ ). However, the authors did not mention details of the types of congenital anomalies and whether they included stillbirth and abortions.<sup>27</sup> The other study reported on 173 major malformations, with 52% involving a single system. The authors stated that although the consanguinity rate was similar (57% vs. 54%), the frequency of the first-cousin type was much higher (51% vs. 30%) in the study group than in the general population.<sup>12</sup> A study from Oman, another country with a high prevalence of consanguinity, reported on 541 major malformations, with 61.9% classified as involvement of a single system. The authors concluded that the consanguinity rate is higher (76%) among parents of those with congenital malformations.<sup>14</sup> Another study from a large Arab village revealed a high rate of congenital malformation resulting from consanguinity.<sup>28</sup> In a 1966 publication from the World Health Organization, summarizing a report on consecutive births from 24 centers, it was concluded that a higher proportion of the parents of malformed children than of normal infants were consanguineous.<sup>29</sup> The same report also pointed out that there was a considerable variation in contribution to the total proportion from different centers, with Alexandria and Bombay being the major contributors. Our study is different from the others

in that it is community based, not hospital based, and representative of the Saudi population. Furthermore, the sample does not include cases of stillbirth or severe cases dying at or shortly after delivery. The sample deals only with isolated and major congenital malformations, excluding mild or multiple congenital anomalies that may be part of an association or a syndrome.

The most important contributor to the list of congenital anomalies was CHD, which is the only congenital malformation in this study for which a statistically significant association with consanguinity was found ( $P=.01$ ). Such a finding supports that of a hospital-based study reporting on a larger sample of children with CHD from Saudi Arabia.<sup>30</sup> The authors found that both all and first-degree cousin types of consanguinity constitute risk factors for CHD, mostly for septal defects. However, the authors pointed out that despite the large sample of cases there was no statisti-

cally significant effect of consanguinity on the occurrence of other congenital heart lesions such as tetralogy of Fallot, patent ductus arteriosus, pulmonary stenosis, pulmonary atresia, aortic stenosis, and coarctation of the aorta. It is of interest that a similar pattern for the effect of consanguinity on CHD was reported from Lebanon.<sup>31</sup> Type 1 diabetes mellitus, the commonest endocrine disease identified in our survey, is another multifactorial disease that was not associated with consanguinity in this study. It can be concluded that the risk of consanguinity is not uniform for all genetic diseases, a fact that should be taken into consideration during genetic counseling.

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